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Ancient and Medieval Chemotherapy for Cancer

By *John M. Riddle*[*]

IN 1916 DR. WILLIAM S. STONE, who became the director for cancer research at New York Memorial Hospital, addressed his colleagues about cancer. Both his own and his father's generation, he explained, treated cancer mostly by surgery; chemical treatments had been virtually abandoned long before. His argument calling for reexamination of the issue was largely historical, based on the observation that classical and early medieval "treatment of the disease . . . almost invariably consist[ed] of arsenic, zinc, or the alkaline caustics." The historical testimony ought to be presumption, he implied, that chemical agents had some beneficial results, even though in his age there had been, in his words, "unqualified condemnation" of them.[1]

Stone's exhortation did not usher in a "second age of chemotherapy" for cancer, however. That age can perhaps be dated to 1938, when A. P. Dustin published his report about the antimitotic properties of colchicine, found in *Colchicum autumnale* L. C. Gordon Zubrod would date modern cancer chemotherapy to about 1935, with the investigation of the effect of bacterial toxins on human sarcomas. Others argue that the true beginning of modern cancer chemotherapy was in World War II, with the research on nitrogen mustards, but, because of security, the results were not published until after the war. Finally, a few note that the experiments by Paul Ehrlich in 1908 on transplantable tumors in rodents anticipated modern chemotherapy.[2] No one, however, disputes that

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[1] W. S. Stone, "A Review of the History of Chemical Therapy in Cancer," *Medical Review,* 7 Oct. 1916, *90*:628–634, quoting pp. 628, 633.

[2] See A. P. Dustin, "Nouvelles applications des poisons caryoclassiques à la cancerologie," *Sang,* 1938, *12*:677–697, based on his earlier study on the mitotic changes induced by colchicine in a rat's Crocker sarcoma: Dustin, "Contribution à l'étude des poisons caryoclassiques sur les tumeurs animales . . . ," *Bulletin de l'Academie Royale de Médecine de Belgique,* 1934, *14*:487–502; on bacterial toxins, see C. Gordon Zubrod, "Origins and Development of Chemotherapy Research at the National Cancer Institute," *Cancer Treatment Reports,* 1984, *68*:9–19, on p. 9; on mustard gas, see Forest Ray Moulton, ed., *Approaches to Tumor Chemotherapy* (Washington, American Association for the Advancement of Science, 1947); and for Ehrlich see Paul Ehrlich, *Experimental Researches on Specific Therapeutics.* (Harben Lectures for 1907) (London: H. K. Lewis, 1908); and Vincent T. DeVita, Jr., "Principles of Chemotherapy," in *Cancer: Principles and Practice of Oncology,* ed. DeVita, Samuel Hellman, and Steven A. Rosenberg, (Philadelphia: Lippincott, 1982), pp. 132–155, on pp. 132–133. A few oncologists look to an earlier remedy as a stimulant to chemical therapy. In 1865 Lissauer ("Zwei Falle von Leucaemie," *Berliner Klinische Wochenschrift,* 1865, *2*:403–404) reported a useful systemic agent in the treatment of neoplastic diseases. The agent was potassium arsenite, which became know as Fowler's solution, but it also produced arsenical keratosis and carcinomas, as reported by Jonathan Hutchinson, "On Some Examples of Arsenic-Keratosis of the

in recent decades complex organic compounds, often plant alkaloids, have produced increasingly successful results as one by one new agents are found and clinically tested.

In 1955 the United States Cancer Chemotherapy National Service Center (NSC) began cataloguing potential plant antitumor agents.[3] Many plants were nominated as candidates for listing by "both the technical literature and folklore." Although historical sources were included under the rubric "folklore," no qualitative historical research was employed to identify potential agents. Many major medical writings were not systematically searched and, for the most part, they were read in translations. The resultant NSC catalogue was impressive in size, but because a single suggestion of a plant in any type of source qualified the plant for the list, so many were listed—over 3,000 species—that using the guide for laboratory testing is difficult.

A more historically oriented approach could well constitute such a guide. A search through the leading pharmaceutical and medical authorities of the Greco-Roman, classical Islamic, and medieval periods reveals that they recommended many of the same natural sources as those for the compounds discovered in the 1960s and 1970s and currently utilized in cancer treatments. For example, in the first century Dioscorides (fl. ca. A.D. 50–79) employed a drug made from autumn crocus (*Colchicum autumnale* L.), the very plant investigated by A. P. Dustin in 1938, as an antitumor agent. Dioscorides recommended that the plant (*kolchikon*) be "soaked in wine and administered to dissolve tumors (*oidêmata*) and growths (*phumata*) not yet making pus."[4] Compounds from this and other plants were neither historically nor are they now the "magic bullet," but they are helpful, sometimes very helpful, in cancer therapy.

"CANCER" IN ANTIQUITY AND THE MIDDLE AGES

Several questions must be answered before recommendations like Dioscorides' can be evaluated, whether historically, for the light they shed on the medicine of the time—especially its probable efficacy—or scientifically, for the direction they might give to current research. First, we need to know whether the ancients had cancers and whether their medicine was capable of distinquishing between benign and malignant neoplasms. The answer to the first question is assuredly affirmative. There is persuasive paleopathological evidence, and such authorities

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Skin and of Arsenic-Cancer," *Transactions of the Pathological Society of London*, 1888, *39*:352–363. For a review of systemic therapy of cancer, see Michael B. Shimkin, *Some Classics of Experimental Oncology: 50 Selections, 1775–1965* (NIH Publication No. 80-2150) (Washington, Department of Health and Human Services, 1980), pp. 651–704.

[3] J. L. Hartwell, "Plants Used Against Cancer," *Lloydia*, 1967, *30*:379–436; 1968, *31*:71–170; 1969, *32*:79–107, 153–205, 247–296; 1970, *33*:97–194, 288–392; 1971, *34*:103–160, 204–255, 310–361, 386–438; reprinted in Hartwell, *Plants Used Against Cancer: A Survey* (Lawrence, Mass.: Quarterman Publications, 1982). For an excellent discussion of advantages and disadvantages of "folklore" nomination of plants for screening, see Matthew Suffness and John Douros, "Drugs of Plant Origin," *Methods in Cancer Research*, 1979, *16*:76–126, on pp. 76–77.

[4] Dioscorides, *De materia medica*, 4.84, ed. Max Wellmann, 3 vols. (Berlin: Weidmann, 1906–1914; rpt. 1958). This and other translations, unless otherwise noted, are my own. For what can be deduced about Dioscorides' life and career, see John Scarborough and Vivian Nutton, "The Preface of Dioscorides' *Materia Medica*: Introduction, Translation, Commentary," *Transactions and Studies of the College of Physicians of Philadelphia*, 1982, N.S. *4*:187–227, on pp. 192–194; and John Riddle, *Dioscorides in Medicine and Pharmacy*, (Austin: Univ. Texas Press, 1985).

as Galen (A.D. 129–post 210) and Avicenna (ca. 980–1037), gave good descriptions of neoplastic tumors.[5] Galen and the Byzantines used the term *onkos* to cover swellings, all types of tumors, and lesions. Ancient and medieval writers employed a variety of terms to describe tumors and other lesions, many of which will be discussed in this article.

From the Hippocratic period, the belief in the etiology of cancer was fairly constant. It was an inflammation (Greek *phlegmonê, phlogôsis*; Latin *inflammatio*) derived from an excess of black bile. Avicenna describes a "malignant" tumor as follows:

> Cancer [*cancer* in Gerard of Cremona's Latin translation] is an atrabilious [black bile] swelling (tumor); its development is from combustible (metabolized) atrabile through a biliary substance or through a substance in which there is a biliary element combusted (metabolized) from it, not through turbid drainage. It differs from *scirrhus* [benign solid tumor which may turn malignant] by being accompanied by pain, acuteness and some degree of beating (throbbing) and rapid growth because of increase of (its) substance and swelling as a manifestation of this substance boiling at its junction with the organ. It differs also (from the scirrhus) by the vessels which formed around it to the organ in which it exists simulating the legs of cancer crab and it is not red as *cellulitis* but "with a trend" to blackness, heat and greenness. . . . And it differs from the true scirrhus by being sensitive while the former has no sensitivity. On its onset it (cancer) is concealed and when it is manifested it is problemic in most cases. Then its signs become apparent. And the initial manifestation is a small solid rounded sprout, dark in color, with some kind of warmth. And there is a kind of cancer that is very painful and there is a kind that produces little pain; silent. And there is a kind of cancer that is unchanged, does not ulcerate.[6]

Galen and Avicenna both characterized most malignant tumors as potentially suppurating, and Galen was especially careful to distinguish suppurating atrabilious metabolizations from those excretions that come from boils, carbuncles, and ulcers.[7]

Greek and Latin had a number of terms that covered malignant tumors; many that may refer to a malignant tumor will be discussed in this article, but only in specific contexts about their therapy. Dioscorides' terms *oidêmata* and *phumata* probably included malignancies, but they were not restricted to that condition. Also there is Galen's Greek term *karkinos* (sometimes *karkinôma*; Latin, *cancer*) which often meant malignant lesions, but not always. Obviously the ancients could not have had the histological diagnosis for malignant neoplasms that we have. We can only conclude that their terms had the lexical range to include malignancies in our sense of the term. In the instance above, Dioscorides probably meant his therapy to apply to malignant neoplastic lesions, for we know the ancients had cancer, that they recognized it (although not precisely), that Dioscorides was correctly pointing to it when he implied suppuration, and that this particular therapy, because of its side effects, would probably not have been resorted to for a benign tumor.

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[5] For paleopathological evidence, see D. Brothwell, in *Diseases in Antiquity* (Springfield: Thomas, 1967), pp. 320–345; Keith Manchester, "Secondary Cancer in an Anglo-Saxon Female," *Journal of Archaeological Science,* 1983, *10*:475–482; Aidan and Eve Cockburn, *Mummies, Disease and Ancient Cultures* (Cambridge, Cambridge Univ. Press, 1983), pp. 37–38; for descriptions, see Galen, *De tumoribus praeter naturam,* in *Opera omnia,* ed. C. G. Kühn, 20 vols. (Leipzig, 1821–1833; Hildesheim: Olms, 1965), Vol. VII, pp. 705–732; Avicenna, *Canon,* 1.2.1.5–4.3.1.15 (Venice, 1507; facs. ed. Hildesheim: Olms, 1964); Aristotelis Eftychaidis, "The Oncology of Nicolaos Myrepsus in Byzantium of the 13th Century" (in Greek), *Hellenic Oncology,* 1981, *17*:38–47, and Eftychaidis, "Oncological Opinions of Byzantine Medical Writers: Neophytus, Maximus Planudes, and John, Bishop of Prisdaunon" (in Greek), *Hell. Onc.,* 1981, *17*:109–116; for an excellent discussion of the Greek terms for cancer, see L. J. Rather, *The Genesis of Cancer: A Study in the History of Ideas* (Baltimore: Johns Hopkins Press, 1978), pp. 9–13.

[6] Avicenna, *Canon,* 4.3.1.15, trans. from Arabic in I. Eltorai, "Avicenna's View on Cancer from his Canon," *American Journal of Chinese Medicine,* 1979, *8*:276–284, quoting from pp. 277, 280.

[7] Galen, *De tumoribus,* 3, in *Opera,* ed. Kühn, Vol. VII, pp. 715–716, trans. in Jeremiah Reedy, "Galen on Cancer and Related Diseases," *Clio Medica,* 1975, *10*:227–238, on p. 232.

Any claim that the ancients had an effective cancer "cure" must be qualified, perhaps even denied. Since Dioscorides gives no information about the exact preparation, concentration of colchicine, dosage, frequency, or administration site, the likely efficacy of his treatment cannot be estimated. Such information, critical to modern evaluations, was not usually given by classical and medieval authorities. Any instructions given are never adequate when judging potential effects of toxic—antimitotic and cytotoxic—drugs employed in cancer therapy. Premodern authorities assumed that their work was to guide those already knowledgeable in the observation of plants (especially proper harvesting periods), drug preparation, dosage, and frequency, as well as in making good diagnoses. Without this information, we can only make informed conjectures about what they were treating and how they were doing it. Autumn crocus contains a sufficient concentration of colchicine for pharmaceutical efficacy, but on the basis of modern studies, we conclude that the drug would arrest tumor mitoses in man but would not produce a complete regression in a malignant tumor.[8] An ancient or medieval physician, treating a malignant growth topically and possibly internally, would probably observe a beneficial response but not a "cure."

Not all early authorities recommended autumn crocus as an antitumor agent. While Dioscorides reported its use, Pliny (A.D. 23–79) recommended it only as an emetic. Galen recommended the plant as a medicine against tumors (*phumata*); Oribasios (325–403) again recommended it only as an emetic. Paulos Aegineta (seventh century) wrote only of its being a "breaking up" agent. Some Latin writers, such as Constantinus Africanus (d. ca. 1087) and Hildegard of Bingen (1098–1178), did not recommend it at all against tumors, despite knowing the plant; Matthaeus Platearius (d. 1161?) and Avicenna employed the plant in ways that suggest antitumoral activity. Platearius, for example, recommends it "contra morbos ex flegmate; . . . . Carnem superfluam corrodit . . . et licinium intinctum fistule imponatur." Abū Manṣūr (fl. 968–977) said that the drug concocted from it is poisonous but dries up old sores.[9] In light of this evidence, one can conclude that prior to the thirteenth century autumn crocus was employed as an anticancer agent, but that its use was not widespread. The reluctance may have been due to the belief expressed by Hildegard, who said that it was more of a poison than a medicine. An interesting and possibly significant footnote: in a field study of traditional medicine in Greece conducted between 1947 and 1960, autumn crocus was reported to be taken internally against cancer.[10]

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[8] The antitumor agent in colchicine is demecolcine (desacetyl-N-methylcolchicine), a bona fide anticancer drug whose use the Federal Drug Administration has not approved in the United States. Because the premodern physicians were dealing with crude drugs, I shall use the broad term colchicine. On demecolcine, see Irving S. Johnson, "Plant Alkaloids," in *Cancer Medicine,* ed. James F. Holland and Emile Frei III, 2nd ed. (Philadelphia: Lea & Febiger, 1982), pp. 910–920. On colchicine, see O. J. Eigsti and Pierre Dustin, Jr., *Colchicine—in Agriculture, Medicine, Biology, and Chemistry* (Ames: Iowa State College Press, 1955), p. 264; and William A. Remers, ed., *Antineoplastic Agents* (New York: Wiley, 1984), p. 214. John Edmund Driver and George E. Trease, *The Chemistry of Crude Drugs* (London: Longmans, Green, 1938), p. 92, give the colchicine concentration in the cormseeds of autumn crocus as between 2% and 8%. Experimental dosages of the cormseeds have ranged from 130 mg to 300 mg; *Dispensatory of the United States of America,* 25th ed. (Philadelphia: Lippincott, 1955), pp. 351–357, on p. 357. Mammary tumors in dogs have been treated with colchicine: 2 dosages of 0.25 mg, 2 dosages of 0.5 mg, and 2 dosages of 1 mg over a six day course, *Merck Index,* 8th ed. (Rahway, N.J.: Merck, 1968), p. 278.

[9] Pliny, *Natural History,* 28.45.160, ed. W. H. S. Jones, 10 vols. (Loeb Classical Library)

METHODOLOGY

In what follows I identify modern agents and then seek their counterpart in the historical records. Some historians may object that it would be better methodology to list all the remedies employed as cancer agents in the historical records and then evaluate them in light of modern medical studies. In general, I agree with the objection, but for the purposes of this article, the better method would produce a much longer study without appreciably different results as to the question whether the premoderns had some effective cancer drugs. A major obstacle is that the longer process would produce many plants that cannot be firmly identified. For instance, in his pharmaceutical treatises, Galen employed only three herbs in the treatment of *oidêmata* (whose meaning we established includes malignant tumors): *akantha(-os) leukê, damasônion,* and *orchis*.[11] The identification of all three is uncertain. *Akantha leukê*—"white thorn"—may be *Acacia albida* Delile, *Euphorbia antiquorum* L., or *Cnicus arvensis* Hoffm., or possibly something else. Each of these is reported in modern studies as being used in various East Asian cultures for cancer therapies. Galen's *damasônion* may be our *Alisma plantago* L., and *orchis* may be either *Ophrys apifera* Huds. or *Orchis* sp. Alisma is reported in modern Chinese medicine as treating leukemia patients effectively, and various species of orchis have been employed for a long period in Western European medicine as an anticancer drug.[12] Beyond problems of plant identification, other uncertainties involved in evaluating Galen's drugs for *oidêmata*, such as uncertain diagnosis and a lack of corresponding modern clinical studies, make difficult even tentative conclusions about these remedies'

(London: Heinemann; Cambridge, Mass.: Harvard Univ. Press, 1938–1962), Vol. VII, p. 110; Galen, *De simplicium medicamentorum temperamentis ac facultatibus,* 6.25, s.v. *ephêmeron* (= *kolchikon*), in *Opera,* ed. Kühn, Vol. XI, pp. 879–880; Paulos Aegineta, *Epitomae medicae,*. 7.3., s.v. *ephêmeron,* trans. Francis Adams, 3 vols. (London: Sydenham Society, 1847), Vol. III, pp. 119–120; Oribasios, *Collectiones medicae reliquae,* 11.29, s.v. *ephêmeron,* ed. Johannes Raeder, 4 vols. (Corpus Medicorum Graecorum, 6.1, 2) (Leipzig: Teubner, 1928–1933), Vol. II, p. 111; Constantinus Africanus, *Liber de gradibus,* in *Opera* (Basel, 1536), p. 379, s.v. *hermodactilus* (= *colchicum*); Hildegard von Bingen, *Physicas,* 2.91, s.v. *hermodactylus* (Strassbourg, 1533); ed. and trans. I. Muller (Salzburg: Muller, 1982), p. 99; Matthaeus Platearius, *Circa instans,* s.v. *hermodactilis,* ed. H. Wölfel (Berlin: Preilipper, 1939), p. 61; Avicenna, *Canon,* 2.2.354, fols. 122v–123r; and Abū Manṣūr Muwaffaq ibn Ali Harāwī, *Die pharmakologischen Grundsätze (Liber fundamentorum pharmacologiae),* trans. Abdul-Chalis Achundow, *Koberts historischen Studien aus dem Pharmakologischen Institute der kaiserlichen Universität Dorpat,* 1893, *3*:137–481, on p. 222, no. 330. Kurt Ruegg, *Beiträge zur Geschichte der officizinellen Drogen: Crocus, Acorus calamus und Colchicum* (Basel: Schahl, 1936), pp. 231–232, believes that Pliny and Galen may have intended *Iris agrestis* rather than *Colchicum autumnale*; however, in my opinion the traditional identification of autumn crocus is correct.

[10] G. Lawrendiadis, "Contribution to the Knowledge of the Medicinal Plants of Greece," *Planta Medica,* 1961, *9*:164–169.

[11] Galen, *De simplicium facultatibus* 6.1, 6.4, 7.15, in *Opera,* ed. Kühn, Vol. XI, pp. 819, 861; Vol. XII, p. 93.

[12] Hartwell, "Plants," *Lloydia,* 1970, *33*:98–99 (*Acacia* sp.); 1969, *32*:159 (*Euphorbia antiquorium*); 1968, *31*: 134, 137, 138, 146 (*Orchis* sp.); 1967, *30*:389 (*Alisma plantago*); 1970, *33*:309 (*Orchis* sp.).

relation to modern scientific studies. A comprehensive approach examining all ancient and medieval anticancer drugs would, I suspect, run into the same problems as those attendant on Galen's *oidêmata* remedies, and the main point would be obscured. If, however, it can be shown that modern chemotherapy agents for cancer were employed in much the same way by ancient and medieval peoples, the case can be made that other drugs which they used and we have not evaluated would be a rational place to begin screening tests.

For example, one ancient and medieval remedy not employed in modern scientific medicine is nightshade (Greek *strychnos*; Latin *solanum* = *Solanum* sp. in Linnean classification). It is a poisonous, alkaloid plant, and Galen thought it especially helpful as an applicant for "ulcerated cancers" (*hêlkêka karkinos*). Dioscorides applied nightshade externally for *erysipelas* and *herpês*. While Pliny gave no specific medicinal uses for it, Celsus applied it on *erysipelas*. Later writers continue the prescription. Today in traditional medicine around the world, nightshade is used to treat cancers, but modern Western medicine does not employ the plant.[13]

Although making an exact count of remedies such as nightshade is impossible, for it would depend on the criteria followed, the number of drugs used in cancer therapy both in modern Western medicine and in ancient and medieval Western medicine is small. One study in 1977 showed only ten plant species employed or being tested in actual clinical studies.[14] While the number of plants used by ancient and medieval authorities is larger, it is not so large that statistical probability alone would account for several drugs used in modern chemotherapy appearing among them, rather than the early authorities' recognition of antitumoral properties. For instance, in the first two books of his work, Dioscorides prescribes only two drugs for *oidêmata*, both in contexts that do not suggest anticancer activity. One, kermes oak, "helps" the tumor, which suggests symptomatic relief; the other, myrrh, is used against tumors caused by poisonous snake bites.[15] He gave only three treatments for *karkinas* (*karkinôma*): frankincense, nettle (*Urtica pilulifera* L. and *U. urens* L.), and figwort (*Scrophularia peregrina* L.).[16] In his entire work, Dioscorides discussed only about seven hundred plants.

ANCIENT AND MEDIEVAL CANCER DRUGS

Of all the classical authorities, only Dioscorides appears to have recognized the actions of plant alkaloids. First he grouped them together by drug affinities: for example, he put plants containing the papaverine alkaloids in one group and those containing tropane alkaloids in another.[17] Second, he employed many of the same plants that we have rediscovered and currently employ. Many of those alkaloids he said were good as antitumor agents. One such plant is the squirting cucumber (*Ecballium elaterium* L.). In 1958 a chemical compound from this plant was found to have "strong antitumor activity against sarcoma."[18] Almost alone among the classical writers, Dioscorides recommended squirting cucumber to "dissolve old, soft tumors (*oidêmata*)." Pliny recommended this same plant as a remedy for a variety of skin conditions, including *psora, lichen,* and *parotis*.[19] These terms may have had the lexical range to encompass malignancies, but Latin and Greek dermatological afflictions are notoriously difficult to translate into modern terminology. For example, Galen said that *psora* was called cancer (*karkinos*), if it "occurred in the veins and flesh."[20] Scribonius Largus (fl. reign of Claudius, A.D. 41–54) prescribed squirting cucumber for *condylomata,* or lumps associated with the anus. These could be malignant anal lesions, but one has no justification to conclude that they were—merely that they could be. Galen, Paulos Aegineta, Cassius Felix (fl. 447), Constantinus Africanus, and Rufinus (fl. 1287) gave no clear recommendations for the plant in conjunction with tumors and neither did such Islamic authorities as Avicenna, Ibn Sarābī (or Serapion, d. ca. 1074), and Māsawaih (or Mesue, 925–1015).[21] This evidence suggests that although the plant was not widely employed against tumors (many of which were malignant lesions), the continuous reliance on the authority of Dioscorides makes it nonetheless likely that there was occasional use of the plant for cancer treatments. This remedy has persisted in folk medicine, so that modern investigators learned in 1952–1953 that the squirting cucumber was taken orally for cancer.[22]

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[13] Galen, *Ad Glauconem de medendi methodo,* 2.12, in *Opera,* ed. Kühn, Vol. XI, p. 143; cf. Galen, *De simplicium facultatibus,* 8.19., s.v. *truchnon ê strychnos*: "*ἕλκη κακοήϑη καὶ νομώδη θεραπεύει,*" *Opera,* ed. Kühn, Vol. XII, p. 146; Dioscorides, *De materia medica,* 4.70, ed. Wellmann, probably for *Solanum nigrum* L.; Pliny, *Natural History,* 27.107.132; Celsus, *De medicina,* 5.26, 33a–b, ed. W. G. Spencer, 2 vols. (Loeb Classical Library) (London: Heinemann; Cambridge: Harvard Univ. Press, 1935–1938), Vol. II, p. 102; Paulos Aegineta, *Epitomae mediciae,* 7.3., s.v. *strychnos*; Platearius, *Circa instans,* 718, ed. Wölfel (cit. n. 13): "contra apostemata in stomacho et intestinis"; Rufinus, *Herbarius,* fol. 104rb–104va, in *The Herbal of Rufinus,* ed. Lynn Thorndike with Francis S. Benjamin, Jr. (Chicago: Univ. Chicago Press, 1945). On modern use for *Solanum dulcamara* L., see George Edward Trease and William C. Evans, *Pharmacognosy,* 11th ed. (London: Tindall, 1978), p. 621.

[14] Walter H. Lewis and M. P. Elvin-Lewis, *Medical Botany* (New York: Wiley, 1977), p. 133.

[15] Dioscorides, *De materia medica,* 1.87, 106, ed. Wellmann.

[16] *Ibid.*, 1.68, 4.93–94.

In the same section of his treatise Dioscorides recommended the bulb of *Narcissus* sp. for a variety of skin afflictions (*epsêlis, alphos, helkos,* and *apostêma*). Narcissus contains colchicine, and an extract from the bulb is employed in modern chemotherapy for cancer. But the plant also contains calcium oxalate, and because some of these afflictions were sores and wounds, the action may have been cleansing owing to the calcium oxalate rather than to antitumoral activity.[23] Also in the same sequence Dioscorides prescribed the castor bean (*Ricinus communis* L.) for *oidêmata* and *erysipelata,* the latter being, according to Galen, a protocancerous condition.[24] The castor bean contains ricin, currently recognized for its antitumorous qualities and employed in cancer chemotherapy research, although because of its high cytotoxicity, present attention is directed towards binding monoclonal antibodies to it to impart tumor specificity.[25] Following his discussion of the castor bean plant, Dioscorides gave a number of recommendations for spurge (*Euphorbia* sp.)—which is in the same family, Euphorbiaceae, as castor bean—as a remedy for afflictions suggestive of cancer. He added that spurge causes loss of hair, weight, and color, and that it even causes death.[26]

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[17] *Ibid.*, 4.63–67 (for papaverine-yielding plants); 4.70–75 (for tropane-yielding plants), ed. Wellmann.

[18] D. Lavie and D. Willner, "The Constituents of *Ecballium elaterium* L. III. Elatericin a and B^{1,2}," *Journal of the American Chemical Society,* 1958, *80*:710–714.

[19] Dioscorides, *De materia medica,* 4.150, ed. Wellmann; Pliny, *Natural History,* 20.2.4, ed. Jones.

[20] Galen, *De tumoribus,* 13, in *Opera,* ed. Kühn, Vol. VII, p. 727; trans. Reedy in "Galen on Cancer" (cit. n. 7), p. 236.

[21] Scribonius Largus, *Compositiones,* 224, ed. Sergio Sconocchia (Leipzig: Teubner, 1983); Galen, *De simplicum facultatibus,* 8.15, s.v. *sikuos* in *Opera,* ed. Kühn, Vol. XII, p. 122; cf. Galen, *Hippocratis Epidemiorum libri II,* 5.7, in *Opera,* Vol. XVIIA, p. 472; Paulos Aegineta, *Epitomae medicae,* 7.3., s.v. *elatêrion*; Cassius Felix, *De medicina,* 8, ed. Valentin Rose (Leipzig: Teubner, 1879), p. 15; Constantinus, *De gradibus* (no entry); Rufinus, *Herbarius* (cit. n. 13), fol. 49vb; Avicenna, *Canon,* 2.2.181, s.v. *cucumer asininus*; Ibn Sarābī, *Simplicibus medicinis,* 196, ed. Otto Brunsfels (Strassbourg, 1531), p. 133; and Māsawaih al-Mārdīnī, *De simplicibus,* 2.7 (Venice, 1558), fol. 64.

[22] Hartwell, "Plants against Cancer," *Lloydia,* 1969, *32*:96, citing the National Cancer Institute's central file.

[23] Dioscorides, *De materia medica,* 4.158, ed. Wellmann; for the narcissus as containing colchicine and calcium oxalate, see Lewis and Elvin-Lewis, *Medical Botany* (cit. n. 14), pp. 135, 78, 80.

Some later writers recommended narcissus, castor bean, and spurge as antitumoral drugs, but many were silent.[27] In one of his pharmaceutical treatises, Galen clearly used narcissus for cleaning wounds (*traumata*) and not as an antitumor agent, but he recommended spurge for a number of types of tumors (*helkos, lichên, psôra, phagedaina, anthrax,* and *gangrainôde*), which in his treatise on tumors he said were often malignant. A preparation of spurge, called *elatêrion,* is given for an incipient cancer (*karkinos genomenos*), according to Galen.[28] Galen described castor bean as good for its dispersing and discutient property (*diaphorêtikos dynamis*), which could very well apply pharmaceutically to antitumoral action, although he did not specify that action, merely the property. Similarly Constantinus Africanus said that spurge was warming and drying to the fourth degree of intensity, thereby making it an extremely dangerous drug, and that it acted to purge black bile and viscous humors.[29] In the context of medieval science, these properties would be sought in a drug against cancer because that disease was in theory an excess of black bile, and any drug having the property of purging black bile would be suitable for testing as an antitumor agent. Drugs so strong in intensity as the fourth degree were considered drastic, life-threatening poisons, to be administered only in extremely severe conditions.[30]

Avicenna recommended narcissus for a variety of dermatological afflictions, none suggestive of cancer, but Rufinus clearly stated that a drug from the plant was applied topically on tumors (*super tumores*). Henri de Mondeville (ca. 1260–1320) prescribed narcissus for indurations and making various tumors soft. On the other hand, Matthaeus Platearius omitted all these poisonous plants, that is narcissus, castor bean, and spurge, from his popular herbal pharmacy. Abū Manṣūr prescribed the castor bean as an antitumor remedy.[31] Some of these drugs, however, are found in folk usages against cancer. The castor bean is or was employed for cancers and tumors in traditional Chinese medicine, Ayurvedic, South American, Indian, San Dominican, and modern Californian folk medicine. Various species of spurge are employed against cancer among the Bantu tribes of South Africa, India, and Finland, among other traditional medicine systems.[32]

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[24] Dioscorides, *De materia medica,* 4.161, ed. Wellmann; Galen, *De tumoribus,* 9, in *Opera,* ed. Kühn, Vol. VII, pp. 723–724; trans. Reedy in "Galen on Cancer" (cit. n. 7), p. 235.

[25] Emil Frei, "Pharmacology," in *Cancer: Achievements, Challenges, and Prospects for the 1980's,* ed. Joseph H. Burchenal and Herbert F. Oettgen, 2 vols. (New York: Grune & Stratton, 1981), Vol. I, pp. 108–122, on p. 113; Lewis and Elvin-Lewis, *Medical Botany* (cit. n. 14), p. 135.

[26] Dioscorides, *De materia medica,* 4.164–169, s.v. *sikuos agrios,* ed. Wellmann.

[27] Hartwell, "Plants against Cancer," *Lloydia,* 1967, *30*:391, citing a quotation in Aetios of Amida, alleges that Soranus recommended narcissus for scirrhous tumors of the uterus. My reading of Soranus's statement was that narcissus was employed as a uterine injection to treat an atonic womb. See Soranus, *Gynecology,* 3.13, trans. Owsei Tempkin (Baltimore: Johns Hopkins Univ. Press, 1956), p. 172; Aetios of Amida recommended narcissus as a cleansing agent in *Libri medicinales,* 1.293, ed. A. Oliveri, 2 vols. (Corpus Medicorum Graecorum, 8) (Leipzig: Teubner), Vol. I (1935), p. 114.

[28] Galen, *De simplicium facultatibus,* 8.13., s.v. *narkissos,* in *Opera,* ed. Kühn, Vol. XII, pp. 85–86; *ibid.,* 8.19., s.v. *tithymalli* (=spurge), in *Opera,* Vol. XII, p. 142; Galen, *Hippocratis Epidemiorum libri II,* 5.8, in *Opera,* Vol. XVIIA, p. 477 (*elatêrion* = a preparation from spurge); on relating terms to cancer, cf. Galen, *De tumoribus,* 6–9, in *Opera,* Vol. IX, pp. 719–724, and trans. Reedy in "Galen on Cancer," pp. 234–235; Galen, *De simplicium facultatibus,* 7.10, s.v. *kikeôs,* in *Opera,* Vol. XII, p. 26.

[29] Galen, *De simplicium facultatibus,* 7.10.24, in *Opera,* ed. Kühn, Vol. XII, p. 26; Constantinus, *De gradibus,* p. 387.

[30] Georg Harig, *Bestimmung der Intensität im medizinischen Systems Galens* (Berlin: Akademie Verlag, 1974); Jerry Stannard, "The Theoretical Bases of Medieval Herbalism," *Medical Heritage,* 1985, *1*:186–198, on 189.

Dioscorides placed yet another plant, *Vinca major* L., in the same sequence with plants containing alkaloids having antitumor activities, but he did not list the plant as specifically active against tumors. Pliny, however, said that *vicapervica* (= *Vinca*) "dried tumors."[33] A genus closely related to *Vinca* is *Catharanthus*. From one of its species, *C. roseus* G. Don, comes the present source for vinblastine and vincristine, which are remarkably effective against acute lymphocytic leukemia, Hodgkin's disease, carcinoma, and lymphosarcoma. Until 1948, *C. roseus* was classified as *Vinca rosa* L.[34] *Vinca major* has no active antitumor compounds, just as Dioscorides observed by omitting this use in discussing the plant. *Vinca* plants were found in the various regions of the eastern Mediterranean where Dioscorides traveled, but *C. roseus* is found in tropical settings, such as Madagascar and India. Many drugs, however, came to the Greeks and Romans from these regions, for example, cassia, cinnamon, and pepper; it is possible that Pliny was referring to a drug taken from the *Catharanthus,* inasmuch as the two genera are so similar that, despite the plant's importance, botanists did not reclassify *Vinca rosa* L. as *Catharanthus roseus* G. Don until recently. Even if Pliny (or his sources) intended the plant that is the source for our cancer therapy, we can be certain that the classical therapeutic use of the catharanthic alkaloids did not have the success that the present therapy has, with its isolation and concentration of active compounds and well-regulated administration. Nonetheless we can hypothesize that some ancient physicians may have observed some beneficial actions as a result of their treating cancers with *Catharanthus*. Possibly their inability to distinguish *Vinca* sp. and *C. roseus* hindered their confidence in the drug derived from the correct species.

Other plants, non-alkaloid-producing but nonetheless toxic, were used against cancers. One, a legume, provides an interesting insight. The plant is one or two species of *Vicia, V. ervilla* L., bitter vetch, or *V. fava* L., horse bean. Its seeds are poisonous but edible if properly prepared and cooked. Dioscorides recommended *Vicia* for "cleaning ulcers with honey, moles (*phakoi*), skin spots (*spiloi*), freckles or rough spots (*ephêles*). . ;. [and] it stops boils/ulcers (*nomai*), gangrene or running sore (*gangraina*); it softens hardness (*sklêriai*) in the breast, malignant ulcers (*thêriôdai*), malignant pustules (*anthrakai*), and *kêria* [= yellow and bad skin swelling or ulcer]."[35] The range of contexts suggests that some of the terms would include cancers, especially deep-seated, papillary, and superficial epithelioma and nonspecific, metastatic inflammatory lesions associated with cancer in the stage of ulceration. The vetch plant (*Vicia* sp.) contains vicianin, a cyanogenic glycoside, and was given for cancer into the nineteenth century.[36] Dioscorides did not recommend apricot pits, the source of amygdalin or laetrile, for cancer. Amygdalin, like vicianin, allegedly is effective because it causes cyanide production upon ingestion. Modern science has not found laetrile an effective antitumor agent despite its popularity in underground medical practices.

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[31] Avicenna, *Canon,* 2.2.514; Rufinus, *Herbarius* (cit. n. 13), fol. 73rb; *Chirurgie de Henri de Mondeville,* 3. Chir. sp. Apostemes. Doct. 2.7.2, 18.2; 4. Doct. 2; Antidotaire. 3.B.2, 5.1, 8.2, 11. 118, ed. A. Bos (Paris, F. Didot, 1897–1898); Abū Manṣūr, *Liber fundamentorum pharmacologiae,* 174, in "Die pharmakologischen Grundsätze," trans. Achundow (cit. n. 9), p. 195.

[32] Hartwell, "Plants against Cancer," *Lloydia,* 1970, *33*:120–122 (castor bean); 158–167 (spurge).

[33] Dioscorides, *De materia medica,* 4.147, s.v. *chamaidaphnê*; and Pliny, *Natural History,* 21.99.172: "vicapervica sive chamaedaphne . . . tumores siccat."

[34] R. L. Noble and Cutts Beer, "Role of Chance Observation in Chemotherapy, *V. rosea,*" *Annals of the New York Academy of Science,* 1958, *76*:882; cf. B. Oliver-Bever, "Vegetable Drugs for Cancer Therapy," *Quarterly Journal of Crude Drug Research,* 1971, *11*:1661–1671, on pp. 1665–1671.

Certainly not all antitumor discoveries were classical. There is at least one fascinating Byzantine modification. An anonymous herbalist called Pseudo-Apuleius, who lived in the fourth century A.D., wrote in Latin that birthwort (*Aristolochia clematitis* L.), commonly recommended for parturition, was good for nasal carcinoma. Although the Greek term *karkinôma* primarily meant malignant tumors, in this case the context suggests a polyp of the nares, usually a benign tumor in the nasal passage, displaying a pedicle, especially on the mucous membrane. Other surviving classical authorities do not ascribe antitumoral qualities to birthwort. But in or before the fourteenth century, a Byzantine commentator added to a text of Dioscorides a statement that birthwort "helps nose [or, skin?] carcinomas (*ἐν ῥινὶ καρκινώμασι βοηθεῖ*)." The Greek word *ῥίς, ῥινός,* means nostril and *ῥινός, ῥινοῦ* means skin. Whether the commentator meant birthwort to be applied to benign nasal tumor or skin cancer is unclear. Whatever the interpretation, another Byzantine scholium sought to strengthen the claim by changing the verb from "it helps" to "it cures (*ἰᾶται*)."[37] In 1969 aristolochic acid from birthwort was found to have antitumoral qualities, and it is now used in cancer chemotherapy.[38]

In 1971 and in 1972, Lee Wattenberg published studies on the effects of cabbage on drug and carcinogen metabolism, and in 1978 he reported that the compounds in cabbage inhibit chemically induced carcinogenesis in rats. In the same year Japanese researchers found antimutagenic action by cabbage juice.[39] While the research on cabbage and other *Brassica* species is promising, the candidacy of drugs from the genus, most especially cabbage, developed late in modern cancer research. But Cato the Elder (234–149 B.C.) spoke of cabbage around 2,200 years ago: "Of the medicinal value of cabbage: It is cabbage which surpasses all other vegetables. . . . It can be used as a poultice on all kinds of wounds and swelling; . . . it will cleanse suppurating wounds and tumors (*vulnera putida canceresque*), and heal them, a thing which no other medicine can do. . . . An ulcer on the breast and a cancer (*in mammis ulceris natum et carcinoma*) can be healed by the application of macerated cabbage." Similarly Dioscorides prescribed that cabbage be applied directly on tumors (*oidêmata*) to cause them to shrink.[40] The therapeutic use of cabbage by the Greek, Roman, and medieval peoples was chiefly as a drug. Modern research investigates it for desmutagenic activity chiefly in diet;[41] this action, prevention of carcinogenesis, is different from the antitumor activity attested by Cato and Dioscorides. Possibly it is only coincidence that ancient and modern attention focused on cabbage. Possibly also the ancients observed that those whose diet was heavy in cabbage were less susceptible to cancers. Possibly cabbage contains an antitumorial compound. The point is that modern attention to it was not, as best as I can determine, first directed by the history of the substance. Most chemotherapeutical agents of today were rediscovered without benefit of history.

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[35] Dioscorides, *De materia medica,* 2.108, ed. Wellmann.

[36] R. J. McIllroy, *The Plant Glycosides* (London: E. Arnold, 1951), pp. 22–23; *Merck Index* (cit. n. 8), 8th ed., p. 1107; cf. 9th ed., pp. 9624–9625; and Hartwell, "Plants against Cancer," *Lloydia,* 1970, *33*:120–122.

[37] Pseudo-Apuleius, *Herbarius,* 19.7, ed. Ernst Howald and Henry Sigerist (Leipzig: Teubner, 1927): "Ad carcinomata, quae in naribus nascuntur. Herba aristolochia cum cipero et draconteae semen cum melle inpositum emendat." The first scholium is found in Paris, BN MS Gr. 2183, (15th c); Venice, San Marco MS Gr. Z 271 (15th c.); and Salamanca MS 2659 (15th c.); the second in Vienna ON MS Gr. 16 (15th c.); and Vatican MS Palatinus Gr. 77 (15th c.). See John M. Riddle, "Byzantine Commentaries on Dioscorides," in *Byzantine Medicine,* ed. John Scarborough (Washington, D.C.: Dumbarton Oaks, 1984), pp. 95–102; see also Schol. Dioscorides, *De materia medica,* 3.4(5), ed. Wellmann, Vol. II, p. 8n (*apparatus criticus* to line 10). On Pseudo-Apuleius, see Linda E. Voigts, "The Significance of the Name *Apuleius* to the *Herbarium Apulei,*" *Bulletin of the History of Medicine,* 1972, *52*:214–227. Pseudo-Apuleius is a highly unlikely source for the Byzantine commentator's scholium because the Latin herbal ascribed to Apuleius had no Greek counterpart or Greek translation.

[38] S. Munavalli and C. Viel, "Etude chimique, taxinomique et pharmacologique des aristolochiacées," *Annales pharmaceutiques français,* 1969, *27*:449–464, on p. 463; Trease and Evans, *Pharmacogonosy* (cit. n. 13), pp. 98, 577; and *Chemical Abstracts,* 1974, *80*:24780g for (*A. baetica*), 1974, *81*:111458z (for *A. clematitis.*)

There are animal sources for drugs as well as plant sources, although many fewer. Traditional Chinese medicine employed a drug made from the blister beetle (*Mylabris phalerata* Pall.) for the treatment of malignant diseases. Dioscorides also said that the drug from the beetle was effective against a malignancy (*karkinôdê*), as well as *lepra* and *leichênê*. Pursuing suggestions from a study of the historical traditions, modern Chinese investigators isolated from the crude drug a compound, cantharidin, that is therapeutic for primary heptocarcinoma, intestinal carcinoma, and other cancerous neoplasms.[42]

[39] L. Wattenberg, "Studies of Polycyclic Hydroxylases of the Intestine Possibly Related to Cancer," *Cancer,* 1972, *28*:99–102; Wattenberg, "Enzymatic reactions and carcinogenesis," in *Enviroment and Cancer* (Baltimore: Williams & Wilkins, 1972), pp. 241–255; Wattenberg and W. D. Loub, "Inhibition of Polycyclic Aromatic Hydrocarbon-induced Neoplasia by Naturally Occurring Indoles," *Cancer Research,* 1978, *38*:1410–1411; T. Kada, K. Morita, and T. Inoue, "Anti-mutagenic Action of Vegetable Factor(s) on the Mutagenic Principle of Tryptophas Pyrolysate," *Mutation Research,* 1978, *53*:351- 353; and K. Morita, M. Hara, and T. Kada, "Studies on Natural Desmutagens," *Agricultural Biological Chemistry,* 1978, *42*(6):1235–1238.

[40] Cato, *On Agriculture,* 156.1.–157.4, ed. and trans. W. D. Hooper and H. B. Ash (Loeb Classical Library) (London: Heinemann; Cambridge, Mass.: Harvard Univ. Press, 1934); and Dioscorides, *De materia medica,* 2.121, ed. Wellmann.

[41] Michael Albert-Puleo, "Physiological Effects of Cabbage with Reference to its Potential as a Dietary Cancer-Inhibitor and its Use in Ancient Medicine," *Journal of Ethnopharmacology,* 1983, *9*:261–272.

[42] Bin Hsu, "The Use of Herbs as Anticancer Agents," *Amer. J. Chin. Med.,* 1980, *8*:304–305; Dioscorides, *De materia medica,* 2.61, ed. Wellmann. On the widespread knowledge and use of cantharidin in Greek and Roman pharmacy, see John Scarborough, "Some Beetles in Pliny's *Natural History,*" *Colepterists Bulletin,* 1977, *31*:293–296, and Scarborough,"Nicander's Toxicology, II: Spiders, Scorpions, Insects and Myriapods," *Pharmacy in History,* 1979, *21*:73–92, on pp. 73–80. Cantharidin is used in the United States pharmacopeia to remove warts, molluscum, and other benign epithelial growths; see *Physicians' Desk Reference,* 37th ed. (Oradell, N.J.: Medical Economics Company, 1983), pp. 827–828, 1882.

In this study I have developed essentially two lines, one modern and the other ancient and medieval, without showing a definite relationship (except in the case of cantharidin). If extreme care is used, the historian can find it useful to evaluate pharmaceutical records in the light of scientific studies, in order to learn whether early practitioners were, in our judgment, "rational" users of medicines. Medical anthropologists have taught us to be cautious because there are many factors that may determine whether a person finds a drug effective. Nonetheless, the historian wishes to know as a matter of curiosity what the physical effects of given drug therapies might have been. Since most of the plants discussed in this paper are sources of alkaloids, which have a toxic effect (cabbage excepted), it is difficult to believe that they could qualify as placebos, at least in the traditional sense. A drug user would seek positive effects to outweigh the deleterious side effects of these toxins. On the other hand, it is probable that premodern users saw some beneficial responses to these drugs when treating tumorous growths, but, since they lacked the ability to control concentration, dosages, and frequencies, the drugs were probably only marginally efficacious.

In contrast, the modern scientist might employ the history of a drug, especially in the works of the leading medical authorities, as a starting point for conducting animal and clinical tests. Important clues exist in the historical records about which drugs might be worth testing. While colchicine is not a drug of choice for cancer therapy, its chemical analogues are employed, and colchicine proved an important first step in modern chemotherapy.[43] William Stone's speech in 1916 was prophetic. For too long we have believed that the past was filled more with superstition and stupidities than with experienced judgments about medicine.

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[43] Remers, *Antineoplastic Agents* (cit. n. 8), p. 214.